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1998wo-us12456.ap.	1

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Search History

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<u>L2</u>	1998wo-us12456.ap.	1	<u>L2</u>
<u>L1</u>	1998wo-us12456.ap,prai.	80	<u>L1</u>

END OF SEARCH HISTORY

Seq #468 AA starts c Met-gly-Phe-Leu

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Search Results - Record(s) 1 through 1 of 1 returned.

☐ 1. Document ID: US 20020161202 A1, WO 9858062 A1, AU 9881447 A, EP 1032661 A1, AU 740227 B, JP 2002508663 W, AU 200213628 A

L2: Entry 1 of 1

File: DWPI

Oct 31, 2002

DERWENT-ACC-NO: 1999-095340

DERWENT-WEEK: 200274

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TITLE: New Apo-2DcR polypeptide - used for modulation and diagnosis of apoptosis, e.g. in neurodegeneration

INVENTOR: ASHKENAZI, A J; BAKER, K P ; CHUNTHARAPAI, A ; GURNEY, A ; KIM, K J ; WOOD, W I

PRIORITY-DATA: 1997US-0878168 (June 18, 1997), 2002AU-0013628 (January 29, 2002), 2001US-0992964 (November 19, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
<u>US 20020161202 A1</u>	October 31, 2002		000	C07K016/46
<u>WO 9858062 A1</u>	December 23, 1998	E	088	C12N015/12
<u>AU 9881447 A</u>	January 4, 1999		000	C12N015/12
<u>EP 1032661 A1</u>	September 6, 2000	E	000	C12N015/12
<u>AU 740227 B</u>	November 1, 2001		000	C12N015/12
<u>JP 2002508663 W</u>	March 19, 2002		127	C12N015/09
<u>AU 200213628 A</u>	March 14, 2002		000	A01K067/027

INT-CL (IPC): A01 K 67/027; A61 K 38/17; C07 K 14/705; C07 K 14/715; C07 K 16/28; C07 K 16/46; C07 K 19/00; C12 N 1/19; C12 N 1/21; C12 N 5/10; C12 N 5/12; C12 N 15/09; C12 N 15/12; C12 N 15/62; C12 P 21/08; G01 N 33/50

ABSTRACTED-PUB-NO: WO 9858062A

BASIC-ABSTRACT:

Isolated Apo-2DcR polypeptide (I) with at least 80% sequence identity with native Apo-2DcR (Ia), comprising a 259 amino acid (aa) sequence (1) given in the specification, is new.

Also new are: (A) isolated extracellular domain (ECD) of (I) comprising aa 1-161 of (1); (B) isolated polypeptide (Ia) comprising aa -40 to 259 of a 299 aa sequence (3) given in the specification; (C) chimeras (II) comprising (I) or its ECD fused to a heterologous aa sequence (III); (D) antibody (Ab) that binds to (I) or its ECD; (E) hybridoma cell lines that produce monoclonal Ab; (F) isolated nucleic acid

(IV) that encodes (I) or its ECD; (G) vector containing (IV); (H) host cell containing this vector; (J) non-human transgenic animal containing cells that express (IV); and (K) non-human knockout animal containing cells with an altered gene for (I).

USE - Host cells of (H) are used to produce recombinant (I) (claimed). (I), and chimeras (II), are used to modulate apoptosis of mammalian cells (claimed) and/or NF-kappaB activation by Apo-2 ligand (ApL) or other ligands, and they may be expressed from (I) for in vivo or ex vivo gene therapy.

(I) are also used as controls in quantitative diagnostic assays; to raise Ab; for affinity purification; in competitive receptor-binding assays and to identify alternative forms of Apo-2DcR.

(IV), and its fragments, are used for diagnostic tissue-typing, and to create the transgenic animals (claimed) (used for screening and development of drugs that protect against excessive apoptosis).

Ab are used: (i) therapeutically to prevent excessive apoptosis, e.g. in cases of neurodegeneration, autoimmune diseases and inflammation, optionally in conjunction with ApL (the bioavailability of which is increased by Ab-mediated blockade of Apo-2DcR); (ii) in tissue staining or immunoassays; and (iii) for affinity purification.

Most human tumour cells do not express Apo-2DcR transcripts, but normal tissues do, suggesting that Apo-2DcR may permit selective killing of cancer cells by ApL, possibly by protecting normal, but not cancerous, cells.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Sequences	Attachments	Claims	KWIC	Drawings
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Terms

Documents

1998wo-us12456.ap.

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PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/12, C07K 14/715, A61K 38/17, C12N 15/62, G01N 33/50, C07K 16/28, A01K 67/027, C12N 5/12	A1	(11) International Publication Number: WO 98/58062 (43) International Publication Date: 23 December 1998 (23.12.98)
(21) International Application Number: PCT/US98/12456 (22) International Filing Date: 12 June 1998 (12.06.98) (30) Priority Data: 08/878,168 18 June 1997 (18.06.97) US (71) Applicant: GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US). (72) Inventors: ASHKENAZI, Avi, J.; 1456 Terrytown Street, San Mateo, CA 94401 (US). BAKER, Kevin, P.; 1115 South Grant Street, San Mateo, CA 94401 (US). CHUNTHARA-PAI, Anan; 826 Ellis Drive, Colma, CA 94015 (US). GURNEY, Austin; 1 Debbie Lane, Belmont, CA 94002 (US). KIM, Kyung, Jin; 622 Benvenue Avenue, Los Altos, CA 94024 (US). WOOD, William, I.; 1400 Terrytown Street, San Mateo, CA 94402 (US). (74) Agents: MARSCHANG, Diane, L. et al.; Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: Apo-2DcR (57) Abstract Novel polypeptides, designated Apo-2DcR, which are capable of binding Apo-2 ligand are provided. Compositions including Apo-2DcR chimeras, nucleic acid encoding Apo-2DcR, and antibodies to Apo-2DcR are also provided.		

its latent form, NF- κ B is complexed with members of the I κ B inhibitor family; upon inactivation of the I κ B in response to certain stimuli, released NF- κ B translocates to the nucleus where it binds to specific DNA sequences and activates gene transcription.

For a review of the TNF family of cytokines and their receptors, see Gruss and Dower, *supra*.

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SUMMARY OF THE INVENTION

Applicants have identified cDNA clones that encode novel polypeptides, designated in the present application as "Apo-2DcR." It is believed that Apo-2DcR is a member of the TNFR family; full-length native sequence human Apo-2DcR polypeptide exhibits similarity to the TNFR family in its extracellular cysteine-rich repeats. Applicants found that Apo-2DcR binds Apo-2 ligand (Apo-2L).

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In one embodiment, the invention provides isolated Apo-2DcR polypeptide. In particular, the invention provides isolated native sequence Apo-2DcR polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 259 of Figure 1A (SEQ ID NO:1). In other embodiments, the isolated Apo-2DcR polypeptide comprises at least about 80% amino acid sequence identity with native sequence Apo-2DcR polypeptide comprising residues 1 to 259 of Figure 1A (SEQ ID NO:1). Optionally, the isolated Apo-2DcR polypeptide includes an amino acid sequence comprising residues identified in Figure 1B as -40 to 259 (SEQ ID NO:3). Optionally, the Apo-2DcR polypeptide is obtained or obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited as ATCC 209087.

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In another embodiment, the invention provides an isolated extracellular domain (ECD) sequence of Apo-2DcR. Optionally, the isolated extracellular domain sequence comprises amino acid residues 1 to 236 of Fig. 1A (SEQ ID NO:1) or residues 1 to 161 of Fig. 1A (SEQ ID NO:1). Optionally, the isolated extracellular domain sequence comprises an amino acid sequence wherein one or more of the amino acids identified in any of the Apo-2DcR pseudorepeats identified herein (See, Figure 2) have been deleted. Such isolated extracellular domain sequences may include polypeptides comprising a sequence of amino acid residues 1 to X, wherein X is any one of amino acid residues 161 to 236 of Figure 1A (SEQ ID NO:1).

20

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In another embodiment, the invention provides chimeric molecules comprising Apo-2DcR polypeptide fused to a heterologous polypeptide or amino acid sequence. An example of such a chimeric molecule comprises an Apo-2DcR fused to an immunoglobulin sequence. Another example comprises an extracellular domain sequence of Apo-2DcR fused to a heterologous polypeptide or amino acid sequence, such as an immunoglobulin sequence.

30

In another embodiment, the invention provides an isolated nucleic acid molecule encoding Apo-2DcR polypeptide. In one aspect, the nucleic acid molecule is RNA or DNA that encodes an Apo-2DcR polypeptide or a particular domain of Apo-2DcR, or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In one embodiment, the nucleic acid sequence is selected from:

35

(a) the coding region of the nucleic acid sequence of Figure 1A (SEQ ID NO:2) that codes for residue 1 to residue 259 (i.e., nucleotides 193-195 through 967-969), inclusive;

(b) the coding region of the nucleic acid sequence of Figure 1A (SEQ ID NO:2) that codes for residue 1 to residue 236 (i.e., nucleotides 193-195 through 898-900), inclusive;

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Genentech, Inc.

(ii) TITLE OF INVENTION: Apo-2DcR

5 (iii) NUMBER OF SEQUENCES: 13

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Genentech, Inc.

(B) STREET: 1 DNA Way

(C) CITY: South San Francisco

10 (D) STATE: California

(E) COUNTRY: USA

(F) ZIP: 94080

(v) COMPUTER READABLE FORM:

15 (A) MEDIUM TYPE: 3.5 inch, 1.44 Mb floppy disk

(B) COMPUTER: IBM PC compatible

(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(D) SOFTWARE: WinPatin (Genentech)

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:

20 (B) FILING DATE: 12-Jun-1998

(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 08/878168

(B) FILING DATE: 18-JUN-1997

25 (viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Marschang, Diane L.

(B) REGISTRATION NUMBER: 35,600

(C) REFERENCE/DOCKET NUMBER: P1110P1PCT

(ix) TELECOMMUNICATION INFORMATION:

30 (A) TELEPHONE: 650/225-5416

(B) TELEFAX: 650/952-9881

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

35 (A) LENGTH: 259 amino acids

(B) TYPE: Amino Acid

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Met Ala Arg Ile Pro Lys Thr Leu Lys Phe Val Val Val Ile Val
 1 5 10 15

40 Ala Val Leu Leu Pro Val Leu Ala Tyr Ser Ala Thr Thr Ala Arg
 20 25 30

Gln Glu Glu Val Pro Gln Gln Thr Val Ala Pro Gln Gln Gln Arg
 35 40 45

	His Ser Phe Lys Gly Glu Glu Cys Pro Ala Gly Ser His Arg Ser	
	50	55 60
	Glu His Thr Gly Ala Cys Asn Pro Cys Thr Glu Gly Val Asp Tyr	
	65	70 75
5	Thr Asn Ala Ser Asn Asn Glu Pro Ser Cys Phe Pro Cys Thr Val	
	80	85 90
	Cys Lys Ser Asp Gln Lys His Lys Ser Ser Cys Thr Met Thr Arg	
	95	100 105
10	Asp Thr Val Cys Gln Cys Lys Glu Gly Thr Phe Arg Asn Glu Asn	
	110	115 120
	Ser Pro Glu Met Cys Arg Lys Cys Ser Arg Cys Pro Ser Gly Glu	
	125	130 135
	Val Gln Val Ser Asn Cys Thr Ser Trp Asp Asp Ile Gln Cys Val	
	140	145 150
15	Glu Glu Phe Gly Ala Asn Ala Thr Val Glu Thr Pro Ala Ala Glu	
	155	160 165
	Glu Thr Met Asn Thr Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu	
	170	175 180
20	Glu Thr Met Asn Thr Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu	
	185	190 195
	Glu Thr Met Thr Thr Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu	
	200	205 210
	Glu Thr Met Thr Thr Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu	
	215	220 225
25	Glu Thr Met Thr Thr Ser Pro Gly Thr Pro Ala Ser Ser His Tyr	
	230	235 240
	Leu Ser Cys Thr Ile Val Gly Ile Ile Val Leu Ile Val Leu Leu	
	245	250 255
30	Ile Val Phe Val	
	259	

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- 35 (A) LENGTH: 1180 base pairs
 (B) TYPE: Nucleic Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

GCTGTGGGAA CCTCTCCACG CGCACGAACT CAGCCAACGA TTTCTGATAG 50

ATTTTGGGA GTTTGACCAG AGATGCAAGG GGTGAAGGAG CGCTTCCTAC 100
 CGTTAGGGAA CTCTGGGGAC AGAGCGCCCC GGCCGCCTGA TGGCCGAGGC 150
 AGGGTGCAGAC CCAGGACCCA GGACGGCGTC GGGAACCATA CC ATG 195
 Met
 5 1
 GCC CGG ATC CCC AAG ACC CTA AAG TTC GTC GTC GTC ATC 234
 Ala Arg Ile Pro Lys Thr Leu Lys Phe Val Val Val Ile
 5 10
 GTC GCG GTC CTG CTG CCA GTC CTA GCT TAC TCT GCC ACC 273
 10 Val Ala Val Leu Leu Pro Val Leu Ala Tyr Ser Ala Thr
 15 20 25
 ACT GCC CGG CAG GAG GAA GTT CCC CAG CAG ACA GTG GCC 312
 Thr Ala Arg Gln Glu Glu Val Pro Gln Gln Thr Val Ala
 30 35 40
 15 CCA CAG CAA CAG AGG CAC AGC TTC AAG GGG GAG GAG TGT 351
 Pro Gln Gln Gln Arg His Ser Phe Lys Gly Glu Glu Cys
 45 50
 CCA GCA GGA TCT CAT AGA TCA GAA CAT ACT GGA GCC TGT 390
 20 Pro Ala Gly Ser His Arg Ser Glu His Thr Gly Ala Cys
 55 60 65
 AAC CCG TGC ACA GAG GGT GTG GAT TAC ACC AAC GCT TCC 429
 Asn Pro Cys Thr Glu Gly Val Asp Tyr Thr Asn Ala Ser
 70 75
 AAC AAT GAA CCT TCT TGC TTC CCA TGT ACA GTT TGT AAA 468
 25 Asn Asn Glu Pro Ser Cys Phe Pro Cys Thr Val Cys Lys
 80 85 90
 TCA GAT CAA AAA CAT AAA AGT TCC TGC ACC ATG ACC AGA 507
 Ser Asp Gln Lys His Lys Ser Ser Cys Thr Met Thr Arg
 95 100 105
 30 GAC ACA GTG TGT CAG TGT AAA GAA GGC ACC TTC CGG AAT 546
 Asp Thr Val Cys Gln Cys Lys Glu Gly Thr Phe Arg Asn
 110 115
 GAA AAC TCC CCA GAG ATG TGC CGG AAG TGT AGC AGG TGC 585
 35 Glu Asn Ser Pro Glu Met Cys Arg Lys Cys Ser Arg Cys
 120 125 130
 CCT AGT GGG GAA GTC CAA GTC AGT AAT TGT ACG TCC TGG 624
 Pro Ser Gly Glu Val Gln Val Ser Asn Cys Thr Ser Trp
 135 140
 GAT GAT ATC CAG TGT GTT GAA GAA TTT GGT GCC AAT GCC 663
 40 Asp Asp Ile Gln Cys Val Glu Glu Phe Gly Ala Asn Ala
 145 150 155
 ACT GTG GAA ACC CCA GCT GCT GAA GAG ACA ATG AAC ACC 702
 Thr Val Glu Thr Pro Ala Ala Glu Glu Thr Met Asn Thr


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160              165              170
AGC CCG GGG ACT CCT GCC CCA GCT GCT GAA GAG ACA ATG 741
Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu Thr Met
              175              180

5  AAC ACC AGC CCA GGG ACT CCT GCC CCA GCT GCT GAA GAG 780
Asn Thr Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu Glu
    185              190              195

ACA ATG ACC ACC AGC CCG GGG ACT CCT GCC CCA GCT GCT 819
Thr Met Thr Thr Ser Pro Gly Thr Pro Ala Pro Ala Ala
10              200              205

GAA GAG ACA ATG ACC ACC AGC CCG GGG ACT CCT GCC CCA 858
Glu Glu Thr Met Thr Thr Ser Pro Gly Thr Pro Ala Pro
    210              215              220

GCT GCT GAA GAG ACA ATG ACC ACC AGC CCG GGG ACT CCT 897
Ala Ala Glu Glu Thr Met Thr Thr Ser Pro Gly Thr Pro
15              225              230              235

GCC TCT TCT CAT TAC CTC TCA TGC ACC ATC GTA GGG ATC 936
Ala Ser Ser His Tyr Leu Ser Cys Thr Ile Val Gly Ile
              240              245

20 ATA GTT CTA ATT GTG CTT CTG ATT GTG TTT GTT T 970
Ile Val Leu Ile Val Leu Leu Ile Val Phe Val
    250              255              259

GAAAGACTTC ACTGTGGAAG AAATTCCTTC CTTACCTGAA AGGTTTCAGGT 1020

AGGCGCTGGC TGAGGGCGGG GGGCGCTGGA CACTCTCTGC CCTGCCTCCC 1070

25 TCTGCTGTGT TCCACAGAC AGAAACGCCT GCCCCTGCCC CAAAAAAAAA 1120

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1170

AAAAAAAAAA 1180

```

(2) INFORMATION FOR SEQ ID NO:3:

```

30 (i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 299 amino acids
    (B) TYPE: Amino Acid
    (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

35 Met Gln Gly Val Lys Glu Arg Phe Leu Pro Leu Gly Asn Ser Gly
    -40              -35              -30

Asp Arg Ala Pro Arg Pro Pro Asp Gly Arg Gly Arg Val Arg Pro
    -25              -20              -15

Arg Thr Gln Asp Gly Val Gly Asn His Thr Met Ala Arg Ile Pro
    -10              -5              1              5

```

Lys Thr Leu Lys Phe Val Val Val Ile Val Ala Val Leu Leu Pro
 10 15 20
 Val Leu Ala Tyr Ser Ala Thr Thr Ala Arg Gln Glu Glu Val Pro
 25 30 35
 5 Gln Gln Thr Val Ala Pro Gln Gln Gln Arg His Ser Phe Lys Gly
 40 45 50
 Glu Glu Cys Pro Ala Gly Ser His Arg Ser Glu His Thr Gly Ala
 55 60 65
 10 Cys Asn Pro Cys Thr Glu Gly Val Asp Tyr Thr Asn Ala Ser Asn
 70 75 80
 Asn Glu Pro Ser Cys Phe Pro Cys Thr Val Cys Lys Ser Asp Gln
 85 90 95
 Lys His Lys Ser Ser Cys Thr Met Thr Arg Asp Thr Val Cys Gln
 100 105 110
 15 Cys Lys Glu Gly Thr Phe Arg Asn Glu Asn Ser Pro Glu Met Cys
 115 120 125
 Arg Lys Cys Ser Arg Cys Pro Ser Gly Glu Val Gln Val Ser Asn
 130 135 140
 20 Cys Thr Ser Trp Asp Asp Ile Gln Cys Val Glu Glu Phe Gly Ala
 145 150 155
 Asn Ala Thr Val Glu Thr Pro Ala Ala Glu Glu Thr Met Asn Thr
 160 165 170
 Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu Glu Thr Met Asn Thr
 175 180 185
 25 Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu Glu Thr Met Thr Thr
 190 195 200
 Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu Glu Thr Met Thr Thr
 205 210 215
 30 Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu Glu Thr Met Thr Thr
 220 225 230
 Ser Pro Gly Thr Pro Ala Ser Ser His Tyr Leu Ser Cys Thr Ile
 235 240 245
 Val Gly Ile Ile Val Leu Ile Val Leu Leu Ile Val Phe Val
 250 255 259

35 (2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1180 base pairs
 - (B) TYPE: Nucleic Acid
 - (C) STRANDEDNESS: Single
 - (D) TOPOLOGY: Linear

40

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GCTGTGGGAA CCTCTCCACG CGCACGAACT CAGCCAACGA TTTCTGATAG 50

ATTTTTGGGA GTTTGACCAG AG ATG CAA GGG GTG AAG GAG 90
Met Gln Gly Val Lys Glu
-40 -35

CGC TTC CTA CCG TTA GGG AAC TCT GGG GAC AGA GCG CCC 129
Arg Phe Leu Pro Leu Gly Asn Ser Gly Asp Arg Ala Pro
-30 -25

CGG CCG CCT GAT GGC CGA GGC AGG GTG CGA CCC AGG ACC 168
Arg Pro Pro Asp Gly Arg Gly Arg Val Arg Pro Arg Thr
-20 -15 -10

CAG GAC GGC GTC GGG AAC CAT ACC ATG GCC CGG ATC CCC 207
Gln Asp Gly Val Gly Asn His Thr Met Ala Arg Ile Pro
-5 1 5

AAG ACC CTA AAG TTC GTC GTC GTC ATC GTC GCG GTC CTG 246
Lys Thr Leu Lys Phe Val Val Val Ile Val Ala Val Leu
10 15

CTG CCA GTC CTA GCT TAC TCT GCC ACC ACT GCC CGG CAG 285
Leu Pro Val Leu Ala Tyr Ser Ala Thr Thr Ala Arg Gln
20 20 25 30

GAG GAA GTT CCC CAG CAG ACA GTG GCC CCA CAG CAA CAG 324
Glu Glu Val Pro Gln Gln Thr Val Ala Pro Gln Gln Gln
35 40

AGG CAC AGC TTC AAG GGG GAG GAG TGT CCA GCA GGA TCT 363
Arg His Ser Phe Lys Gly Glu Glu Cys Pro Ala Gly Ser
45 50 55

CAT AGA TCA GAA CAT ACT GGA GCC TGT AAC CCG TGC ACA 402
His Arg Ser Glu His Thr Gly Ala Cys Asn Pro Cys Thr
60 65 70

GAG GGT GTG GAT TAC ACC AAC GCT TCC AAC AAT GAA CCT 441
Glu Gly Val Asp Tyr Thr Asn Ala Ser Asn Asn Glu Pro
75 80

TCT TGC TTC CCA TGT ACA GTT TGT AAA TCA GAT CAA AAA 480
Ser Cys Phe Pro Cys Thr Val Cys Lys Ser Asp Gln Lys
85 90 95

CAT AAA AGT TCC TGC ACC ATG ACC AGA GAC ACA GTG TGT 519
His Lys Ser Ser Cys Thr Met Thr Arg Asp Thr Val Cys
100 105

CAG TGT AAA GAA GGC ACC TTC CGG AAT GAA AAC TCC CCA 558
Gln Cys Lys Glu Gly Thr Phe Arg Asn Glu Asn Ser Pro
110 115 120

GAG ATG TGC CGG AAG TGT AGC AGG TGC CCT AGT GGG GAA 597

Glu Met Cys Arg Lys Cys Ser Arg Cys Pro Ser Gly Glu
 125 130 135
 GTC CAA GTC AGT AAT TGT ACG TCC TGG GAT GAT ATC CAG 636
 Val Gln Val Ser Asn Cys Thr Ser Trp Asp Asp Ile Gln
 5 140 145
 TGT GTT GAA GAA TTT GGT GCC AAT GCC ACT GTG GAA ACC 675
 Cys Val Glu Glu Phe Gly Ala Asn Ala Thr Val Glu Thr
 150 155 160
 CCA GCT GCT GAA GAG ACA ATG AAC ACC AGC CCG GGG ACT 714
 10 Pro Ala Ala Glu Glu Thr Met Asn Thr Ser Pro Gly Thr
 165 170
 CCT GCC CCA GCT GCT GAA GAG ACA ATG AAC ACC AGC CCA 753
 Pro Ala Pro Ala Ala Glu Glu Thr Met Asn Thr Ser Pro
 175 180 185
 GGG ACT CCT GCC CCA GCT GCT GAA GAG ACA ATG ACC ACC 792
 15 Gly Thr Pro Ala Pro Ala Glu Glu Thr Met Thr Thr
 190 195 200
 AGC CCG GGG ACT CCT GCC CCA GCT GCT GAA GAG ACA ATG 831
 20 Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu Glu Thr Met
 205 210
 ACC ACC AGC CCG GGG ACT CCT GCC CCA GCT GCT GAA GAG 870
 Thr Thr Ser Pro Gly Thr Pro Ala Pro Ala Ala Glu Glu
 215 220 225
 ACA ATG ACC ACC AGC CCG GGG ACT CCT GCC TCT TCT CAT 909
 25 Thr Met Thr Thr Ser Pro Gly Thr Pro Ala Ser Ser His
 230 235
 TAC CTC TCA TGC ACC ATC GTA GGG ATC ATA GTT CTA ATT 948
 Tyr Leu Ser Cys Thr Ile Val Gly Ile Ile Val Leu Ile
 240 245 250
 GTG CTT CTG ATT GTG TTT GTT T GAAAGACTTC ACTGTGGAAG 990
 30 Val Leu Leu Ile Val Phe Val
 255 259
 AAATTCCTTC CTTACCTGAA AGGTTTCAGGT AGGCGCTGGC TGAGGGCGGG 1040
 GGGCGCTGGA CACTCTCTGC CCTGCCTCCC TCTGCTGTGT TCCCACAGAC 1090
 35 AGAAACGCCT GCCCTGCCC CAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1140
 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1180

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- 40 (A) LENGTH: 43 base pairs
 (B) TYPE: Nucleic Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TGTAAACGA CGGCCAGTTA AATAGACCTG CAATTATTAA TCT 43

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 41 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

10 CAGGAAACAG CTATGACCAC CTGCACACCT GCAAATCCAT T 41

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 49 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His
1 5 10 15

20 Leu Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly
20 25 30

Gln Val Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys
35 40 45

Gly Cys Arg Lys
49

25 (2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Cys Asn Pro Cys Thr Glu Gly Val Asp Tyr Thr Asn Ala Ser Asn
1 5 10 15

Asn Glu Pro Ser Cys Phe Pro Cys Thr Val Cys Lys Ser Asp Gln
20 25 30

35 Lys His Lys Ser Ser Cys Thr Met Thr Arg Asp Thr Val Cys Gln
35 40 45

Cys Lys Glu

48

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 70 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGGAGCCGCT CATGAGGAAG TTGGGCCTCA TGGACAATGA GATAAAGGTG 50
10 GCTAAAGCTG AGGCAGCGGG 70

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 1799 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CCCACGCGTC CGCATAAATC AGCACGCGGC CGGAGAACCC CGCAATCTCT 50
GCGCCACAA AATACACCGA CGATGCCCGA TCTACTTTAA GGGCTGAAAC 100
20 CCACGGGCCT GAGAGACTAT AAGAGCGTTC CCTACCGCC ATG GAA 145
Met Glu
1
CAA CGG GGA CAG AAC GCC CCG GCC GCT TCG GGG GCC CGG 184
Gln Arg Gly Gln Asn Ala Pro Ala Ala Ser Gly Ala Arg
25 5 10 15
AAA AGG CAC GGC CCA GGA CCC AGG GAG GCG CGG GGA GCC 223
Lys Arg His Gly Pro Gly Pro Arg Glu Ala Arg Gly Ala
20 25
AGG CCT GGG CTC CGG GTC CCC AAG ACC CTT GTG CTC GTT 262
30 Arg Pro Gly Leu Arg Val Pro Lys Thr Leu Val Leu Val
30 35 40
GTC GCC GCG GTC CTG CTG TTG GTC TCA GCT GAG TCT GCT 301
Val Ala Ala Val Leu Leu Leu Val Ser Ala Glu Ser Ala
45 50
35 CTG ATC ACC CAA CAA GAC CTA GCT CCC CAG CAG AGA GCG 340
Leu Ile Thr Gln Gln Asp Leu Ala Pro Gln Gln Arg Ala
55 60 65
GCC CCA CAA CAA AAG AGG TCC AGC CCC TCA GAG GGA TTG 379
Ala Pro Gln Gln Lys Arg Ser Ser Pro Ser Glu Gly Leu

	70	75	80	
	TGT CCA CCT GGA CAC CAT ATC TCA GAA GAC GGT AGA GAT	418		
	Cys Pro Pro Gly His His Ile Ser Glu Asp Gly Arg Asp	85 90		
5	TGC ATC TCC TGC AAA TAT GGA CAG GAC TAT AGC ACT CAC	457		
	Cys Ile Ser Cys Lys Tyr Gly Gln Asp Tyr Ser Thr His	95 100 105		
	TGG AAT GAC CTC CTT TTC TGC TTG CGC TGC ACC AGG TGT	496		
10	Trp Asn Asp Leu Leu Phe Cys Leu Arg Cys Thr Arg Cys	110 115		
	GAT TCA GGT GAA GTG GAG CTA AGT CCC TGC ACC ACG ACC	535		
	Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr	120 125 130		
	AGA AAC ACA GTG TGT CAG TGC GAA GAA GGC ACC TTC CGG	574		
15	Arg Asn Thr Val Cys Gln Cys Glu Glu Gly Thr Phe Arg	135 140 145		
	GAA GAA GAT TCT CCT GAG ATG TGC CGG AAG TGC CGC ACA	613		
	Glu Glu Asp Ser Pro Glu Met Cys Arg Lys Cys Arg Thr	150 155		
20	GGG TGT CCC AGA GGG ATG GTC AAG GTC GGT GAT TGT ACA	652		
	Gly Cys Pro Arg Gly Met Val Lys Val Gly Asp Cys Thr	160 165 170		
	CCC TGG AGT GAC ATC GAA TGT GTC CAC AAA GAA TCA GGC	691		
25	Pro Trp Ser Asp Ile Glu Cys Val His Lys Glu Ser Gly	175 180		
	ATC ATC ATA GGA GTC ACA GTT GCA GCC GTA GTC TTG ATT	730		
	Ile Ile Ile Gly Val Thr Val Ala Ala Val Val Leu Ile	185 190 195		
	GTG GCT GTG TTT GTT TGC AAG TCT TTA CTG TGG AAG AAA	769		
30	Val Ala Val Phe Val Cys Lys Ser Leu Leu Trp Lys Lys	200 205 210		
	GTC CTT CCT TAC CTG AAA GGC ATC TGC TCA GGT GGT GGT	808		
	Val Leu Pro Tyr Leu Lys Gly Ile Cys Ser Gly Gly Gly	215 220		
35	GGG GAC CCT GAG CGT GTG GAC AGA AGC TCA CAA CGA CCT	847		
	Gly Asp Pro Glu Arg Val Asp Arg Ser Ser Gln Arg Pro	225 230 235		
	GGG GCT GAG GAC AAT GTC CTC AAT GAG ATC GTG AGT ATC	886		
40	Gly Ala Glu Asp Asn Val Leu Asn Glu Ile Val Ser Ile	240 245		
	TTG CAG CCC ACC CAG GTC CCT GAG CAG GAA ATG GAA GTC	925		
	Leu Gln Pro Thr Gln Val Pro Glu Gln Glu Met Glu Val	250 255 260		

CAG GAG CCA GCA GAG CCA ACA GGT GTC AAC ATG TTG TCC 964
 Gln Glu Pro Ala Glu Pro Thr Gly Val Asn Met Leu Ser
 265 270 275

5 CCC GGG GAG TCA GAG CAT CTG CTG GAA CCG GCA GAA GCT 1003
 Pro Gly Glu Ser Glu His Leu Leu Glu Pro Ala Glu Ala
 280 285

GAA AGG TCT CAG AGG AGG AGG CTG CTG GTT CCA GCA AAT 1042
 Glu Arg Ser Gln Arg Arg Arg Leu Leu Val Pro Ala Asn
 290 295 300

10 GAA GGT GAT CCC ACT GAG ACT CTG AGA CAG TGC TTC GAT 1081
 Glu Gly Asp Pro Thr Glu Thr Leu Arg Gln Cys Phe Asp
 305 310

GAC TTT GCA GAC TTG GTG CCC TTT GAC TCC TGG GAG CCG 1120
 Asp Phe Ala Asp Leu Val Pro Phe Asp Ser Trp Glu Pro
 15 315 320 325

CTC ATG AGG AAG TTG GGC CTC ATG GAC AAT GAG ATA AAG 1159
 Leu Met Arg Lys Leu Gly Leu Met Asp Asn Glu Ile Lys
 330 335 340

20 GTG GCT AAA GCT GAG GCA GCG GGC CAC AGG GAC ACC TTG 1198
 Val Ala Lys Ala Glu Ala Ala Gly His Arg Asp Thr Leu
 345 350

TAC ACG ATG CTG ATA AAG TGG GTC AAC AAA ACC GGG CGA 1237
 Tyr Thr Met Leu Ile Lys Trp Val Asn Lys Thr Gly Arg
 355 360 365

25 GAT GCC TCT GTC CAC ACC CTG CTG GAT GCC TTG GAG ACG 1276
 Asp Ala Ser Val His Thr Leu Leu Asp Ala Leu Glu Thr
 370 375

CTG GGA GAG AGA CTT GCC AAG CAG AAG ATT GAG GAC CAC 1315
 Leu Gly Glu Arg Leu Ala Lys Gln Lys Ile Glu Asp His
 30 380 385 390

TTG TTG AGC TCT GGA AAG TTC ATG TAT CTA GAA GGT AAT 1354
 Leu Leu Ser Ser Gly Lys Phe Met Tyr Leu Glu Gly Asn
 395 400 405

GCA GAC TCT GCC WTG TCC TAAGTGTG ATTCTCTTCA GGAAGTGAGA 1400
 35 Ala Asp Ser Ala Xaa Ser
 410 411

CCTTCCCTGG TTTACCTTTT TTCTGGAAAA AGCCCAACTG GACTCCAGTC 1450

AGTAGGAAAG TGCCACAATT GTCACATGAC CGGTACTGGA AGAAACTCTC 1500

CCATCCAACA TCACCCAGTG GATGGAACAT CCTGTAACTT TTTACTGCAC 1550

40 TTGGCATTAT TTTTATAAGC TGAATGTGAT AATAAGGACA CTATGGAAAT 1600

GTCTGGATCA TTCCGTTTGT GCGTACTTTG AGATTTGGTT TGGGATGTCA 1650

TTGTTTTCAC AGCACTTTT TATCCTAATG TAAATGCTTT ATTTATTTAT 1700
 TTGGGCTACA TTGTAAGATC CATCTACAAA AAAAAAAAAA AAAAAAAG 1750
 GGCGGCCGCG ACTCTAGAGT CGACCTGCAG AAGCTTGGCC GCCATGGCC 1799

(2) INFORMATION FOR SEQ ID NO:11:

- 5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 411 amino acids
 (B) TYPE: Amino Acid
 (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

10	Met	Glu	Gln	Arg	Gly	Gln	Asn	Ala	Pro	Ala	Ala	Ser	Gly	Ala	Arg	1	5	10	15
	Lys	Arg	His	Gly	Pro	Gly	Pro	Arg	Glu	Ala	Arg	Gly	Ala	Arg	Pro	20	25	30	
15	Gly	Leu	Arg	Val	Pro	Lys	Thr	Leu	Val	Leu	Val	Val	Ala	Ala	Val	35	40	45	
	Leu	Leu	Leu	Val	Ser	Ala	Glu	Ser	Ala	Leu	Ile	Thr	Gln	Gln	Asp	50	55	60	
	Leu	Ala	Pro	Gln	Gln	Arg	Ala	Ala	Pro	Gln	Gln	Lys	Arg	Ser	Ser	65	70	75	
20	Pro	Ser	Glu	Gly	Leu	Cys	Pro	Pro	Gly	His	His	Ile	Ser	Glu	Asp	80	85	90	
	Gly	Arg	Asp	Cys	Ile	Ser	Cys	Lys	Tyr	Gly	Gln	Asp	Tyr	Ser	Thr	95	100	105	
25	His	Trp	Asn	Asp	Leu	Leu	Phe	Cys	Leu	Arg	Cys	Thr	Arg	Cys	Asp	110	115	120	
	Ser	Gly	Glu	Val	Glu	Leu	Ser	Pro	Cys	Thr	Thr	Thr	Arg	Asn	Thr	125	130	135	
	Val	Cys	Gln	Cys	Glu	Glu	Gly	Thr	Phe	Arg	Glu	Glu	Asp	Ser	Pro	140	145	150	
30	Glu	Met	Cys	Arg	Lys	Cys	Arg	Thr	Gly	Cys	Pro	Arg	Gly	Met	Val	155	160	165	
	Lys	Val	Gly	Asp	Cys	Thr	Pro	Trp	Ser	Asp	Ile	Glu	Cys	Val	His	170	175	180	
35	Lys	Glu	Ser	Gly	Ile	Ile	Ile	Gly	Val	Thr	Val	Ala	Ala	Val	Val	185	190	195	
	Leu	Ile	Val	Ala	Val	Phe	Val	Cys	Lys	Ser	Leu	Leu	Trp	Lys	Lys	200	205	210	
	Val	Leu	Pro	Tyr	Leu	Lys	Gly	Ile	Cys	Ser	Gly	Gly	Gly	Gly	Asp				

	215	220	225
	Pro Glu Arg Val Asp Arg Ser Ser Gln Arg Pro Gly Ala Glu Asp		
	230	235	240
5	Asn Val Leu Asn Glu Ile Val Ser Ile Leu Gln Pro Thr Gln Val		
	245	250	255
	Pro Glu Gln Glu Met Glu Val Gln Glu Pro Ala Glu Pro Thr Gly		
	260	265	270
	Val Asn Met Leu Ser Pro Gly Glu Ser Glu His Leu Leu Glu Pro		
	275	280	285
10	Ala Glu Ala Glu Arg Ser Gln Arg Arg Arg Leu Leu Val Pro Ala		
	290	295	300
	Asn Glu Gly Asp Pro Thr Glu Thr Leu Arg Gln Cys Phe Asp Asp		
	305	310	315
15	Phe Ala Asp Leu Val Pro Phe Asp Ser Trp Glu Pro Leu Met Arg		
	320	325	330
	Lys Leu Gly Leu Met Asp Asn Glu Ile Lys Val Ala Lys Ala Glu		
	335	340	345
	Ala Ala Gly His Arg Asp Thr Leu Tyr Thr Met Leu Ile Lys Trp		
	350	355	360
20	Val Asn Lys Thr Gly Arg Asp Ala Ser Val His Thr Leu Leu Asp		
	365	370	375
	Ala Leu Glu Thr Leu Gly Glu Arg Leu Ala Lys Gln Lys Ile Glu		
	380	385	390
25	Asp His Leu Leu Ser Ser Gly Lys Phe Met Tyr Leu Glu Gly Asn		
	395	400	405
	Ala Asp Ser Ala Xaa Ser		
	410 411		

(2) INFORMATION FOR SEQ ID NO:12:

- (i) SEQUENCE CHARACTERISTICS:
- 30 (A) LENGTH: 29 base pairs
- (B) TYPE: Nucleic Acid
- (C) STRANDEDNESS: Single
- (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

35 ATCAGGGACT TTCCGCTGGG GACTTTCCG 29

(2) INFORMATION FOR SEQ ID NO:13:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 base pairs

(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

5 AGGATGGGAA GTGTGTGATA TATCCTTGAT 30